IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: J. Zara
Ian MacLachlan, *et al.*	Art Unit: 1635
Application No.: 09/243,102	Declaration of Mark Murray Under 37 C.F.R. §1.132
Filed: February 2, 1999	
For: SYSTEMIC DELIVERY OF SERUM STABLE PLASMID LIPID PARTICLES FOR CANCER THERAPY	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Mark Murray, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true.

2. I hold a Ph.D. (1978) from the University of Oregon Health Sciences University, and a M.S. (1973) from the University of San Francisco. I am presently the President and Chief Executive Officer for Protiva Biotherapeutics, Inc. (Burnaby, Canada).

My field of expertise is molecular oncogenesis and protein therapy. I have authored nineteen publications in the fields of molecular oncogenesis and protein therapy. A true copy of my *Curriculum Vitae* is attached hereto as Exhibit A.

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

3. The present invention is directed to methods of treating tumors in mammals by delivery of serum stable nucleic acid-lipid particles with a nucleic acid portion that is fully encapsulated within the lipid portion. The delivery of serum stable nucleic acid-lipid particles is by injection at an injection site that is distal to the tumor in the mammal. The lipid portion of the nucleic acid-lipid particle comprises a cationic lipid, a neutral lipid, and a lipid that prevents aggregation during formulation.

4. I have read and am familiar with the contents of the subject patent application. I have also read the Office Action received from the United States Patent and Trademark Office dated October 3, 2002. It is my understanding that the Examiner is concerned that the claimed methods (1) are not enabled by the specification; and (2) are anticipated. Specifically, the Examiner states that the Applicants have demonstrated (1) numerous examples of successful *in vitro* and *in vivo* delivery of nucleic acids using the nucleic acid-lipid particles describe herein and (2) the ability to treat various tumor models *in vivo* using the claimed methods. However, the Examiner alleges that the specification is not enabling for (1) treatment of any neoplasm by distal administration of any nucleic acid fully encapsulated within any nucleic acid-lipid particle and (2) nucleic acid-lipid particles comprising any lipid formulation.

5. This declaration is provided to demonstrate that practice of the claimed methods is fully enabled by the specification and that the claimed methods are not anticipated. This declaration presents (1) additional experiments in which nucleic acids fully encapsulated in lipid formulations are expressed in cells upon transfection; (2) additional experiments in which nucleic acid-lipid particles inhibited tumor growth after administration to mice seeded with tumors; and (3) multiple lipid formulations for use in nucleic acid-lipid particles. The results unequivocally demonstrate that (1) nucleic acids encapsulated in the nucleic acid-lipid particles of the present invention are effectively expressed for treatment of neoplasia; (2) administration of the nucleic acid-lipid particles of the present invention is effective for treating tumors; and (3) multiple lipid

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

formulations can be used for the lipid portion of the nucleic acid-lipid particles. One of skill in the art can therefore practice the claimed methods using information provided in the specification, together with methodology known to one of skill in the art at the time of the present invention, with at most, only routine experimentation.

6. The models used in carrying out the experiments described below are art-accepted models for (1) measuring transfection of cells with nucleic acids and (2) treating tumors. As demonstrated by the examples, (1) nucleic acids encapsulated in the lipid portion of the nucleic-acid lipid particles of the present invention are expressed in tumor cells and (2) the methods of the present invention are effective for treating tumors by distal administration of expressible genes fully encapsulated within the nucleic acid-lipid particles disclosed and claimed in the patent application.

7. As discussed with the Examiners during the interview of June 11, 2003, one advantage of the nucleic acid-lipid particles is tumor specific expression of nucleic acids encapsulated in the lipid portion of the nucleic acid-lipid particle. Additional experiments which are not described in the specification demonstrate that nucleic acids fully encapsulated in the nucleic acid-lipid particles of the present invention are expressed in tumor cells, but not in normal tissues. Two sets of experiments were conducted and are described below.

In the first set of experiments, mice were seeded with tumor cells. The mice were then intravenously injected with a nucleic acid-lipid particle containing a plasmid encoding luciferase. The mice were sacrificed and expression of luciferase was determined. Luciferase expression was observed in the tumor cells, but no significant luciferase expressed was observed in liver, spleen, lung, or kidney. A graphic illustration of the results is shown as Exhibit B.

In the second set of experiments, mice were seeded with tumor cells. The mice were then intravenously injected with a nucleic acid-lipid particle containing a plasmid encoding luciferase. The mice were sacrificed and expression of luciferase was

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

determined. Luciferase expression was observed in the tumor cells, but no significant luciferase expression was observed in spleen, liver, adrenal glands, small intestine, thymus, lymph node, testes, kidney, heart, lung, large intestine, bone, or brain. A graphic illustration of the results is shown as Exhibit C.

These experiments demonstrate that delivery of any nucleic acid encapsulated in the nucleic acid-lipid particles disclosed and claimed in the patent application will lead to specific expression of the nucleic acid in tumor cells.

8. Additional experiments which are not described in the specification demonstrate that nucleic acids fully encapsulated in the nucleic acid-lipid particles of the present invention are actually expressed. Four sets of experiments were conducted and are described below.

In the first set of experiments, mice were seeded with neuroblastoma cells. The mice were then intravenously injected with a nucleic acid-lipid particle containing a plasmid encoding luciferase. The mice were sacrificed and expression of luciferase was determined. Luciferase expression was observed in the neuroblastoma cells.

In the second set of experiments, mice were seeded with melanoma cells. The mice were then intravenously injected with a nucleic acid-lipid particle containing a plasmid encoding luciferase. The mice were sacrificed and expression of luciferase was determined. Luciferase expression was observed in the melanoma cells.

The third set of experiments, mice were seeded with glioblastoma cells. The mice were then intravenously injected with a nucleic acid-lipid particle containing a plasmid encoding luciferase. The mice were sacrificed and expression of luciferase was determined. Luciferase expression was observed in the glioblastoma cells.

In the fourth set of experiments, mice were seeded with fibrosarcoma cells. The mice were then intravenously injected with a nucleic acid-lipid particle containing a plasmid encoding luciferase. The mice were sacrificed and expression of luciferase was determined. Luciferase expression was observed in the fibrosarcoma cells.

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

These examples unequivocally establish that administration of nucleic acid-lipid particles as claimed in the present invention leads to expression of the nucleic acid fully encapsulated in the nucleic acid-lipid particles.

9. In addition to the extensive examples in the specification showing that growth of multiple tumor types is inhibited or reduced by administration of nucleic acid-lipid particles using the presently claimed methods, results from continuing experiments demonstrate that the growth of additional tumor types are inhibited by delivery of the nucleic acid-lipid particles using the presently claimed methods. In particular, growth of neuroblastoma, K1735 melanoma, and Harding Passey melanoma have all been shown to be inhibited.

10. Three additional sets of experiments, which again use art-accepted tumor models, demonstrate the efficacy of the nucleic acid-lipid particles administered using the presently claimed methods. These experiments, which were not described in the specification, are described below.

In the first set of experiments, mice were seeded subcutaneously with Neuro 2A neuroblastoma cells. On day 5 and every other day following for eight days, empty nucleic acid-lipid particles or nucleic acid-lipid particles containing a nucleic acid encoding HSV-TK were intravenously administered to the mice. Beginning on day 5 and every day following, mice were treated intraperitoneally with lipid formulated ganciclovir once daily. Mice treated with HSV-TK in nucleic acid-lipid particles and ganciclovir exhibited a marked reduction in tumor growth rate. A graphic illustration of the results is attached as Exhibit D.

In the second set of experiments, mice were seeded subcutaneously with Harding Passey melanoma cells. On day 17 and every other day following for eight days, empty nucleic acid-lipid particles or nucleic acid-lipid particles containing a nucleic acid encoding HSV-TK were intravenously administered to the mice. Beginning on day 19 and every day following, mice were treated intraperitoneally with ganciclovir once daily.

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

Mice treated with HSV-TK in nucleic acid-lipid particles and ganciclovir exhibited a marked reduction in tumor growth rate. A graphic illustration of the results is attached as Exhibit E.

In the third set of experiments, mice were seeded subcutaneously with K1735 melanoma cells. On day 12 and every other day following for eight days, empty nucleic acid-lipid particles or nucleic acid-lipid particles containing a nucleic acid encoding HSV-TK were intravenously administered to the mice. Beginning on day 14 and every day following, mice were treated intraperitoneally with ganciclovir once daily. Mice treated with HSV-TK in nucleic acid-lipid particles and ganciclovir exhibited a marked reduction in tumor growth rate. A graphic illustration of the results is attached as Exhibit F.

These experiments demonstrate that nucleic acid-lipid particles delivered according to the presently claimed methods are effective for inhibiting growth of additional tumor types when administered at a site distal to the tumor. In particular, these experiments demonstrate that, administration of fully encapsulated nucleic acids encoding are effective in inhibiting tumor growth.

11. As explained above, the lipid portion of the nucleic acid-lipid particles of the presently claimed invention comprises a cationic lipid, a neutral lipid and a lipid that prevents aggregation during formulation (*i.e.*, a fusion regulating lipid). Multiple cationic lipids, neutral lipids, and fusion regulating lipids can be used in the nucleic acid-lipid particles in which the nucleic acid is fully encapsulated in the lipid portion of the particle as disclosed and claimed in the present invention. The ratio of cationic lipids to neutral lipids to fusion regulating lipids can also be varied in the nucleic acid-lipid particles of the claimed invention. Suitable cationic lipids include, but are not limited to DODAC, DODMA and its derivatives, DOTAP, DOPC, and DC-Chol. Suitable neutral lipids include but are not limited to DOPE, DSPC, and cholesterol. Suitable lipids that prevent aggregation include, but are not limited to PEG-lipids such as PEG Ceramides, PEG-diacylglycerols, PEG-DSA derivatives as well as PEO lipid

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

derivatives. Thus, multiple lipid formulations can be used in the nucleic acid-lipid particles of the presently claimed invention. For example, at least twenty five representative lipid formulations (including fourteen different options for cationic lipid components, seven different options for neutral lipid components, and eleven options for lipids that prevent aggregation during formulation) that have actually been used to make lipid portions of nucleic acid lipid particles used in the presently claimed invention. A chart summarizing these formulations is attached as Exhibit G.

12. It is my understanding that in the Office Action mailed October 3, 2002, the Examiner cited two references that allegedly anticipate the claimed methods: Kirn *et al.*, (U.S. Patent No. 6,133,243) and Hung *et al.* (U.S. Patent No. 6,197,754).

Kirn *et al.* disclose nucleic acid-lipid complexes. More particularly, Kirn *et al.* describe preparation of nucleic acid-lipid complexes by first preparing cationic liposomes. Only after the liposomes are fully formed are they mixed with nucleic acids to form nucleic acid-lipid complexes (*see, e.g.*, col. 11, line 65 to col. 12, line 61). Thus, in contrast to the nucleic-acid lipid particles used in the methods of the present invention, the nucleic acid-lipid complexes of Kirn *et al.* do not comprise a nucleic acid fully encapsulated in the lipid portion of a nucleic-acid lipid particle.

Hung *et al.* disclose nucleic acid-lipid complexes. More particularly, Hung *et al.*, describe preparation of nucleic acid-lipid complexes by first preparing cationic liposomes. Only after the liposomes are fully formed are they mixed with nucleic acids to form nucleic acid-lipid complexes (*see, e.g.*, col. 38, line 58 to col. 39, line 30). Thus, in contrast to the nucleic-acid lipid particles used in the methods of the present invention, the nucleic acid-lipid complexes of Hung *et al.* do not comprise a nucleic acid fully encapsulated in the lipid portion of a nucleic-acid lipid particle.

Thus, neither of the cited references anticipate the claimed methods of treating tumors in mammals by delivering serum stable nucleic acid-lipid particles comprising a nucleic acid portion that is fully encapsulated within the lipid portion.

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

13. In view of the foregoing, it is my scientific opinion that one of skill in the art would be able to practice the claimed invention with, at most, routine experimentation using the guidance in the specification and what is known to those of skill in the art. The specification, therefore, fully enables the methods of the invention.

In addition, it is my scientific opinion that neither Kirn *et al.* nor Hung *et al.* describe methods of treating tumors in mammals by delivery of serum stable nucleic acid-lipid particles with a nucleic acid portion that is fully encapsulated within the lipid portion. Thus, neither of the cited references anticipate the claimed invention.

Dated: June 29, 2003 By:_____
Mark J. Murray, Ph.D.

SF 1472666 v1

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

Exhibit A

Mark J. Murray, Ph.D.
1127 41st Ave. E.
Seattle, WA. 98112

PROFESSIONAL EXPERIENCE

PROTIVA BIOTHERAPEUTICS INC. — **June 2000 - Present**
President and Chief Executive Officer

STEM CELL PHARMACEUTICALS — **Jan - June 2000**
Vice President, Business Development

XCYTE THERAPIES, Seattle, WA — **1997- Dec 1999**
Vice President, Business Development

ZYMOGENETICS INC., Seattle, WA. — **1982 - 1997**
Vice President, Strategic Business Development — *1995 - 1997*
Senior Director, New Business Development — *1993 - 1995*
Director, New Business Development — *1989 - 1992*
R&D Manager, Wound Repair Program — *1987 - 1989*
Project Leader — *1983 - 1987*
Senior Scientist — *1982 - 1983*

GRADUATE ACADEMIC EXPERIENCE

Postdoctoral Fellow — *1979 - 1982*
Center for Cancer Research, Massachusetts Institute of Technology
Dr. Robert A. Weinberg, Supervisor

Postdoctoral Fellow — *1978 - 1979*
University of Oregon Health Sciences University
Dr. David Kabat, Supervisor

Ph.D. Candidate — *1975 - 1978*
University of Oregon Health Sciences University
Dr. David Kabat, Supervisor

Masters Degree Candidate — *1971 - 1973*
Department of Biology, University of San Francisco
Dr. C. Peter Flessel, Supervisor

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

SCIENTIFIC PUBLICATIONS

Murray, M.J. and C.P. Flessel (1976). Metal-polynucleotide interactions: A comparison of carcinogenic and non-carcinogenic metals in *vitro. Biochim. Biophys. Acta* **425**, 256-261.

Burns, R.P., I.K. Gipson and M.J. Murray. Keratopathy in tyrosinemia. *In: The Eye and Inborn Errors of Metabolism,* D. Bergman, A. Bron and E. Cotlier (eds.), Alan Liss, New York, 1976.

Murray, M.J., and D. Kabat (1979). Genetic and sialylation sources of heterogeneity of murine leukemia virus membrane envelope glycoproteins gp69/71. *J. Biol. Chem.* **254,** 1340-1348.

Ruta, M., M.J. Murray, M.C. Webb and D. Kabat (1979). A murine leukemia virus mutant with a temperature-sensitive defect in the synthesis of the membrane envelope glycoprotein. *Cell* **16,** 77-88.

Dresler, S., M. Ruta, M.J. Murray and D. Kabat (1979). A glycoprotein encoded by the Friend spleen focus-forming virus. *J. Virol* 30, 564-575.

Kabat, D., M. Ruta, M.J. Murray and E. Polonoff (1980). Immunoselection of mutants deficient in cell surface glycoprotein encoded by murine erythroleukemia viruses. *PNAS* **77,** 57-61.

Shih, C., L. Padhy, M.J. Murray and R.A. Weinberg (1981). Transforming genes of carcinomas and neuroblastomas into mouse fibroblasts. *Nature* **290**, 261-264.

Murray, M.J., B.C. Shilo, C. Shih, D. Cowing, H.W., Hsu and R.A. Weinberg (1981). Three different human tumor cell lines contain different oncogenes. *Cell* **25,** 355-361.

Toole, J.J., B. Z. Shilo, M.J. Murray, C. Shih and R.A. Weinberg (1981). Molecular determinants of human carcinogenesis. Colonic Carcinogenesis: Falk Symposium 31, MTP Press Limited, Lancaster, England.

Murray, M.J., C. Shih, L.F. Parada, C. Tabin and R.A. Weinberg (1983). Characterization of human tumor cell transforming genes. *In: Tumor Viruses and Differentiation.* UCLA Symposia on Molecular and Cellular Biology, Vol. 5.

Murray, M.J., R.J. Kaufman, S.A. Latt and R.A. Weinberg (1983). Construction and use of a dominant, selectable marker: A. Harvey Sarcoma Virus - dihydrofolate reductase chimera. *Mol. and Cell Biol.* **3,** 32-53.

Murray, M.J., J. Cunningham, L. Parada, F. Dautry, P. Lebowitz and R.A. Weinberg (1983). The HL-60 Transforming Sequence: A *ras* oncogene coexisting with altered *myc* genes in hematopoietic tumors. *Cell* **33,** 749-757.

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

Martinville, B., J. Cunningham, M.J. Murray and U. Franke (1983). The N-*ras* oncogene assigned to the short arm of human chromosome 1. *Nucl. Acids Res.* **11**, 5267-5275.

Kelly, J., E. Raines, R. Ross and M.J. Murray (1985). The B-Chain of PDGF alone is sufficient for mitogenesis. *EMBO J.* **4**, 3399-3405.

O'Hara, P.J., F.J. Grant, B.A. Haldeman, C.L. Gray, M.Y. Insley. F.S. Hagen and M.J. Murray (1987). Nucleotide sequence of the gene coding for human factor VII, a vitamin K-dependent protein participating in blood coagulation. *PNAS* **84**, 5158-5162.

Gronwald, R.G.K., F.J. Grant, B. Haldeman, C.E. Hart, P. O'Hara, F.S. Hagen, R. Ross, D.F. Bowen-Pope and M.J. Murray (1988). Cloning and expression of a cDNA coding for the human platelet-derived growth factor receptor: Evidence for more than one receptor class. *PNAS* **85**, 3435-3439.

Hart, C.E., J.W. Forstrom, J.D. Kelly, R.A. Seifert, R.A. Smith, R. Ross, M.J. Murray and D.F. Bowen-Pope (1988). Two classes of PDGF receptor recognize different isoforms of PDGF. *Science* **240**, 1529-1531.

Murray, M.J., B. A. Haldeman, F.J. Grant and P.J. O'Hara (1988). Probing the human genome with minisatellite-like sequences from the human coagulation Factor VII gene. *Nucl. Acids Res.* **16**, 4166.

Seifert, R.A., C. E. Hart, P. E. Phillips, J.W. Forstrom. R. Ross, M.J. Murray and D.F. Bowen-Pope (1989). Two different subunits associate to create isoform-specific PDGF receptors. *J. Biol. Chem.* **264**, 8771-8778.

Hart, C. E., J.W. Forstrom, J. D. Kelly, R.A. Smith, R. Ross, M.J. Murray and D.F. Bowen-Pope (1989). Biochemical evidence for multiple classes of platelet-derived growth factor receptor. *In: Growth Factors and their Receptors: Genetic Control and Rational Application,* R. Ross, A.W. Burgess and T. Hunter (eds.), Alan R. Liss, Inc., New York 297-305.

Richey, K.J., L.H. Engrav, E.G. Pavlin, M.J. Murray, J.R. Gottlieb and M.D. Walkinshaw (1989). Topical growth factors and wound contraction in the rat: part I. Literature review and definition of the rat model. *Ann. Plast. Surg.* **23**, 159.

Engrav, L.H., K.J. Richey, C.C. Kao and M.J. Murray (1989). Topical growth factors and wound contraction in the rat: part II. Platelet-derived growth factor and wound contraction in normal and steroid-impaired rats. *Ann. Plast. Surg.* **23**, 245.

Clark, R.A.F., J.M. Folkvard, C.E. Hart, M.J. Murray, J.M. McPherson (1989). Platelet isoforms of platelet-derived growth factor stimulate fibroblasts to contract collagen matrices. *J. Clin. Invest.* **84**, 1036.

Hart, C.E., J.W. Forstrom, J.D. Kelly, R.A. Smith, R. Ross, M.J. Murray and D.F. Bowen-Pope (1989). Biochemical evidence for multiple classes of platelet-derived growth factor receptor. *In: Growth Factors and their Receptors: Genetica Control and Rational*

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

Application, R. Ross, A.W. Gurgess and T. Hunter (eds.), Alan R. Liss, Inc., New York, 297-305.

Greenhalgh, D.G., K.H. Sprugel, M.J. Murray and R. Ross (1990). PDGF and FGF stimulate wound healing in the genetically diabetic mouse. *Am. J. Path.* **136**, 1235-1246.

Mehmet, H., E. Nanberg, W. Lehmann, M.J. Murray and E. Rozengurt (1990). Early signals in the mitogenic response of Swiss 3T3 cells: A comparative study of purified PDGF homodimers. *Growth Fact.* 3, 83-95.

Ferns, G.A.A., Sprugel, K.H., Seifert, R.A., Bowen-Pope, D.F., Kelly, J.D., Murray, M.J. Raines, E.W. and Ross, R. (1990). Relative platelet-derived growth factor receptor subunit expression determines cell migration to different dimeric forms of PDGF. *Growth Fact.*, 3, 315-324.

Sprugel, K.H., Greenhalgh, D.G., Murray, M.J. and Ross, R. (1991). Platelet-derived growth factor and impaired wound healing. *In: Clinical and Experimental Approaches to Dermal and Epidermal Repair: Normal and Chronic Wounds* (Alan R. Liss, Inc.).

Ogawa, Y., Ksander, G.A., Pratt, B.M., Sawamura, S.J., Ziman, J.M., Gerhardt, C.O., Avis, P.D., Murray, M.J., and McPherson, J.M. (1991). Differences in the biological activities of transforming growth factor-β and platelet-derived growth factor *in vivo*. *Growth Fact.* 5, 57-68.

ABSTRACTS OF MEETING PRESENTATIONS

Brooksby, G.A. and M.J. Murray. Role of activation of sympathetic nervous system on anterior uveal blood flow. ARVO meeting, April 1974 (invited lecture).

Beard, M.E., C.H. Lobitz, M.J. Murray and K.D. Weupper. Tyrosine-induced keratopathy in the decomplemented rat. ARVO meeting, April 1974 (invited lecture).

Brooksby, G.A. and M.J. Murray. Role of autonomic nervous system in control of anterior uveal blood flow. Meetings of the Pacific Coast Section of ARVO, September, 1975.

Murray, M.J., I.K. Gipson and J.D. Wolfe-Lande. Biochemical aspects of tyrosine-induced keratopathy. ARVO meeting, September, 1975 (poster).

Tabin, C., S. Goff, M. Murray, D. Baltimore and R.A. Weinberg. Transfection of cloned retroviral DNA's and selectable markers. Cold Spring Harbor RNA Tumor Virus meeting, 1981 (poster).

Murray, M.J., D. Cowing and R.A. Weinberg. The use of a retrovirus transcriptional promoter to activate a dihydrofolate reductase cDNA in mammalian cells. Cold Spring Harbor RNA Tumor Virus meeting, 1981 (poster).

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

Murray, M.J., C. Shih, J. Toole, M. McCoy, B. Shilo and R.A. Weinberg. Transforming genes of human tumor cell lines. Second Annual Congress for Recombinant DNA Research, Los Angeles, February, 1982 (invited lecture).

Murray, M.J., C. Shih, J. Toole, M. McCoy and R.A. Weinberg. Oncogenes of human tumor cells. Symposium on Chemical Carcinogenesis. Department of Pathology and Jonsson Comprehensive Cancer Center, UCLA, February, 1982 (invited lecture).

Murray, M.J., C. Shih, L.F. Parada, C. Tabin and R.A. Weinberg. Characterization of human tumor cell transforming genes. Cetus-UCLA Symposuim, Tumor Viruses and Differentiation, Squaw Valley, May, 1982 (invited lecture).

Murray, M.J. and J.D. Kelly. Expression of the B-chain of PDGF in yeast, evidence for B-chain mitogenesis. ICN-UCLA Symposium, Oncogenes and their Products, February 1985.

Murray, M.J., J.D. Kelly, E. Raines and J. Forstrom. Expression of the B-chain of PDGF in Yeast. 1986 Gordon Conference on Growth Factors (poster).

Sprugle, K.H., E.W. Raines, J.D. Kelly, M.J. Murray and R. Ross. Chemotactic activity of PDGF-related sequences expressed in yeast. 1986 American Society of Cellular Biology meeting (invited lecture).

McPherson, J., B. Pratt, Y. Ogawa, S. Sawamura, G. Kasander, J. Forstrom and M.J. Murray. A comparison of the biological activities of PDGF-BB and TGF-β1 *in vivo*. UCLA Symposium, Keystone, 1988 (poster).

Hart, C., J. Forstrom, J. Kelly, R. Smith, R. Ross, M.J. Murray and D. Bowen-Pope. Multiple classes of PDGF receptor recognize different isoforms of PDGF. UCLA Symposium, Keystone, 1988, (invited lecture).

Ogawa, Y., S.J. Sawamura, B.M. Pratt, J.M. McPherson, M.J. Murray and G.A. Ksander. Transforming growth factor-β induces accumulation of hyaluronate *in vivo*. American Society of Cell Biology, San Francisco, 1989. (invited lecture)

ISSUED U.S. PATENTS

Murray et al., Expression of Biologically Active PDGF Analogs in Eucaryotic Cells, No. 5,187,263, Issued February 16, 1993

Murray et al., Expression of Biologically Active PDGF Analogs in Eucaryotic Cells, No. 4,766,073, Issued August 23, 1988

Murray et al., Biologically Active PDGF Derived A-chain Homodimers, No. 4,889,919, Issued December 26, 1989

Murray et al., Biologically Active B-chain Homodimers, No. 5,516,896, Issued May 14, 1996

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

Murray et al., Biologically Active Mosaic Proteins, No. 5,498,600, Issued March 12, 1996

Murray et al., Biologically Active B-chain Homodimers, No. 5,428,010, Issued June 27, 1995

Murray et al., Biologically Active B-chain Homodimers, No. 4,845,075, Issued July 4, 1989

Foster et al., Expression of Protein C, No. 4,959,318, Issued September 25, 1990

Kelly et al., Methods for Detecting PDGF Agonist or Antagonist Activity Using PDGF α-Receptor, No. 5,618,678, Issued April 8, 1997

Foster et al., Production of Activated Protein C, No. 5,516,650, Issued May 14, 1996

Murray et al., PDGF Analogs and Methods of Use, No. 5,474,982, Issued December 12, 1995

Murray et al., PDGF Analogs and Methods of Use, No. 5,128,321, Issued July 7, 1992

Murray et al., Expression of Biologically Active PDGF Analogs in Eucaryotic Cells, No. 4,801,542, Issued January 31, 1989

Murray et al., Expression of Biologically Active PDGF Analogs in Yeast, No. 4,769,328, Issued September 6, 1988

Murray et al, Expression of Biologically Active PDGF Analogs in Eucaryotic Cells, No. 5,045,633, Issued September 3, 1991

PENDING U.S. PATENT APPLICATIONS

Murray et al., Biologically Active A-chain Homodimers, No. 08/412,551, Allowed.

Four pending U.S. Patent Applications related to PDGF

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

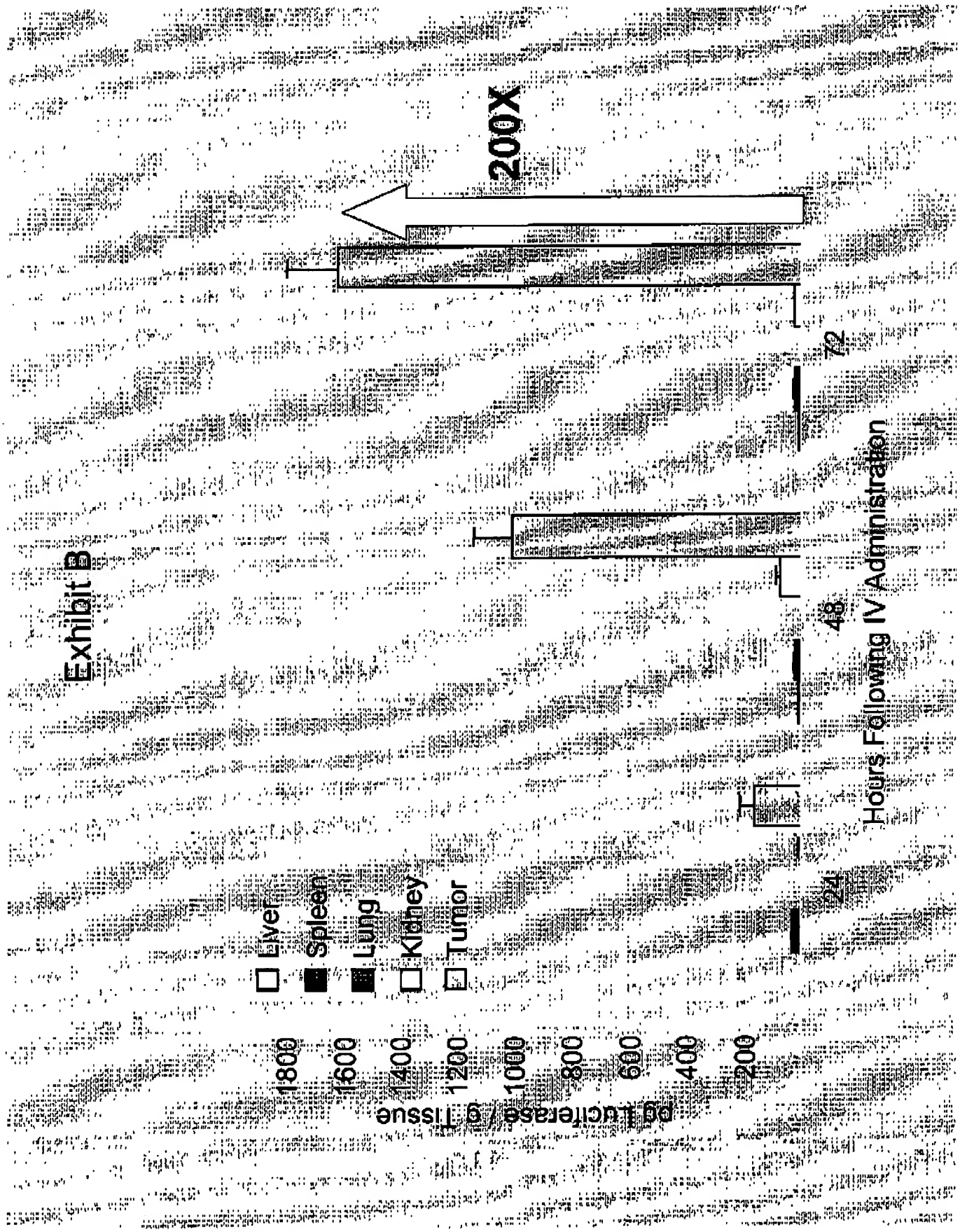
Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

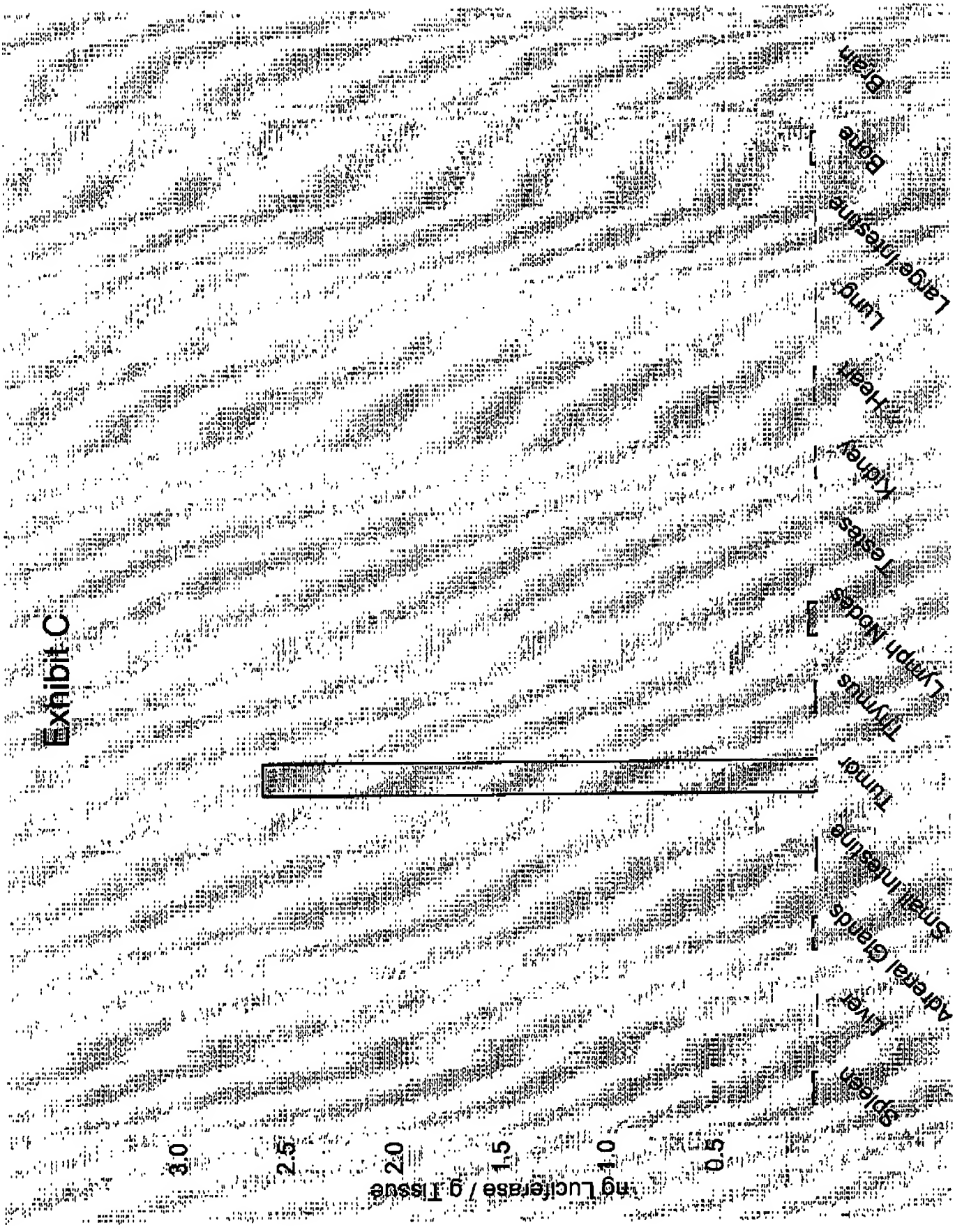
- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.



Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]



Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

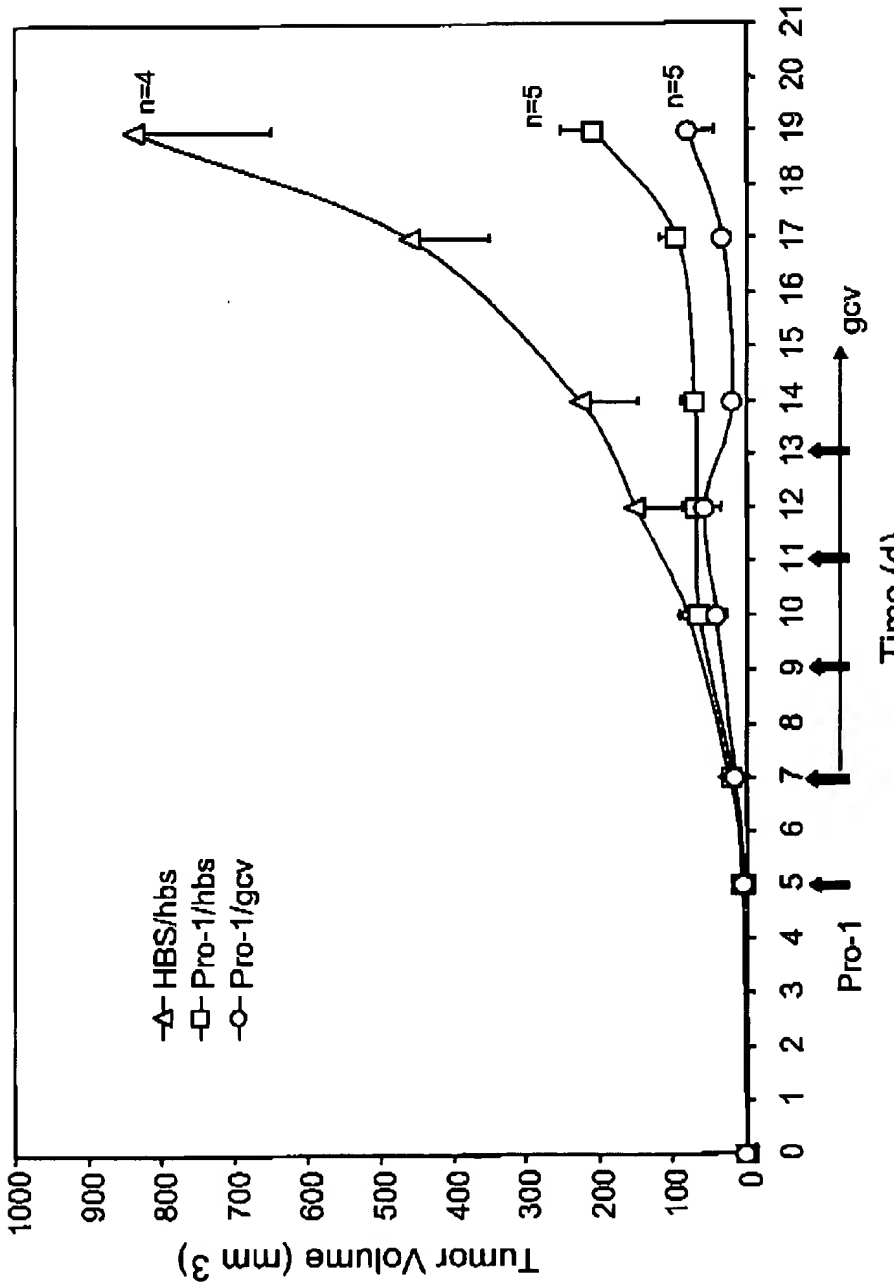


Exhibit D

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

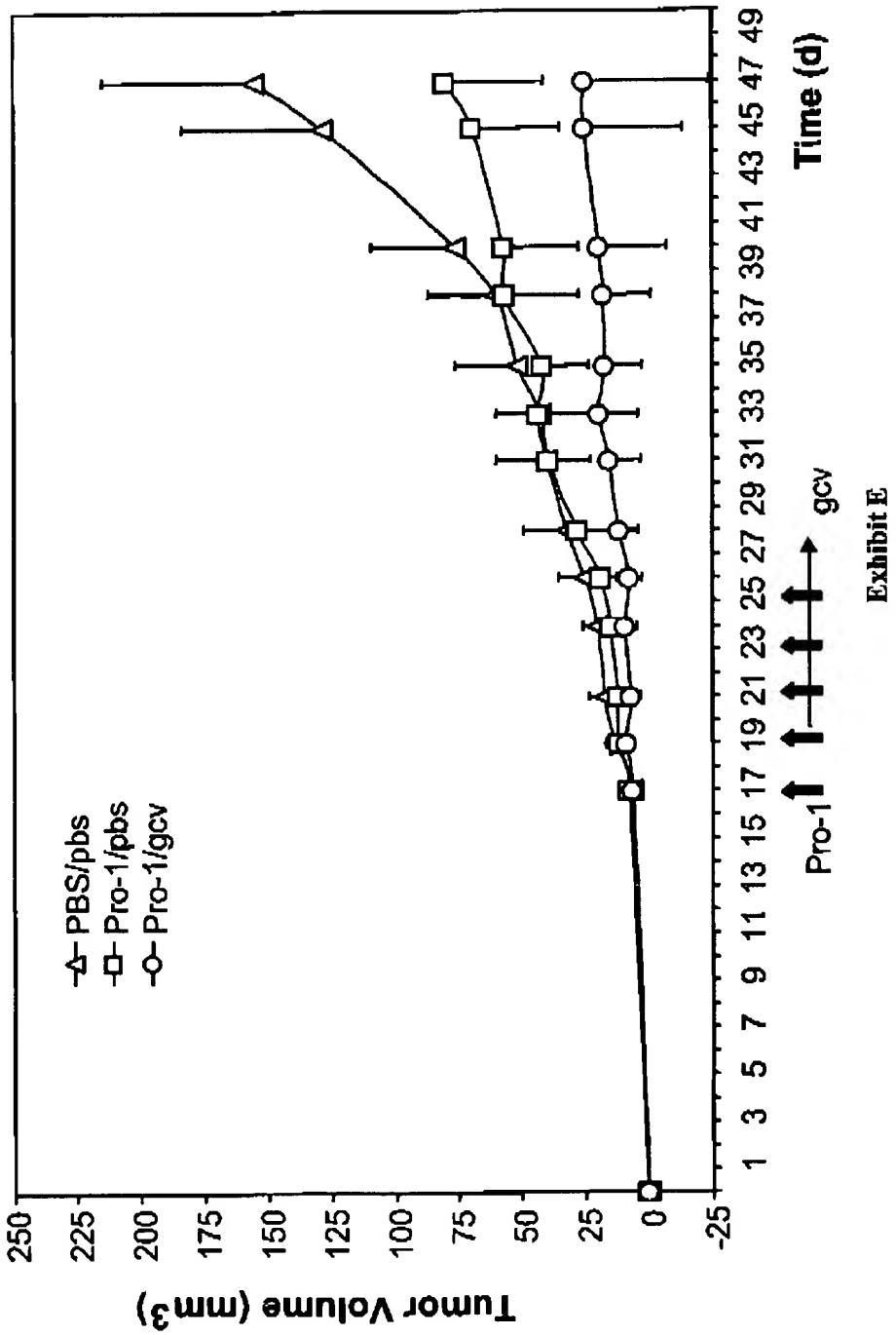


Exhibit E

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

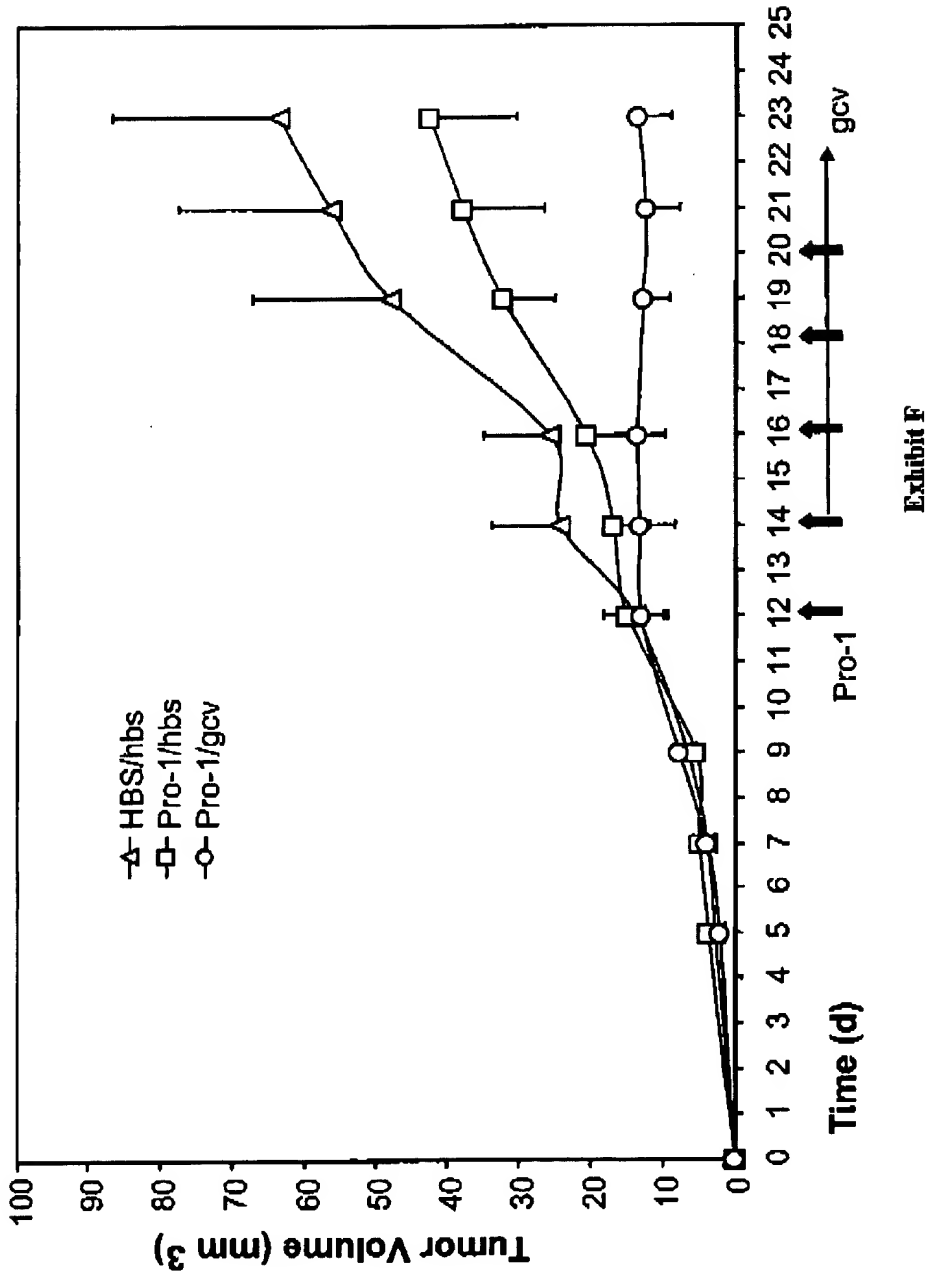


Exhibit F

Received from < 415 576 0300 > at 6/30/03 11:40:47 AM [Eastern Daylight Time]

Received from <415 576 0300> at 6/30/03 11:40:47 AM [Eastern Daylight Time]

06/30/2003 08:39 FAX 415 576 0300

Exhibit G

#	Cationic Lipid(s) (mol%)	Neutral Lipid(s) (mol%)	Fusion Regulator(s) (mol%)
1	DODAC (7.5)	DOPE (82.5)	PEGCeramideC20 (10)
2	DODAC (7.5)	DOPE (82.5)	PEG-DSG (10)
3	DODAC (7.5)	DOPE (82.5)	PEG-DPG (10)
4	DODAC (7.5)	DOPE (82.5)	PEG-DMG (10)
5	DODAC (12)	DOPE (78)	PEGCeramideC20 (10)
6	ethyl-DOPC (8)	DOPE (82)	PEGCeramideC20 (10)
7	DOTAP (8)	DOPE (82)	PEGCeramideC20 (10)
8	DOTAP (12)	DOPE (78)	PEGCeramideC20 (10)
9	DOTAP (16)	DOPE (74)	PEGCeramideC20 (10)
10	DC-Chol (8)	DOPE (82)	PEGCeramideC20 (10)
11	DC-Chol (12)	DOPE (78)	PEGCeramideC20 (10)
12	DC-Chol (16)	DOPE (74)	PEGCeramideC20 (10)
13	DC-Chol (20)	DOPE (70)	PEGCeramideC20 (10)
14	DODMA-AN (8)	DOPE (82)	PEGCeramideC20 (10)
15	DODMA-AN (12)	DOPE (78)	PEGCeramideC20 (10)
16	DODMA (25)	DSPC (20) Cholesterol (45)	PEG-DSG (10)
17	DODMA (15)	DSPC (20) Cholesterol (55)	PEG-DSG (10)
18	DODMA (15)	DSPC (20) Cholesterol (55)	PEGCeramideC20 (10)
19	DODMA (15)	DSPC (20) Cholesterol (55)	PEG-A-DMA (10)
20	DODMA (15)	DSPC (20) Cholesterol (55)	PEG-A-DPA (10)
21	DODMA (15)	DSPC (20) Cholesterol (55)	PEG-A-DSA(10)
22	DODMA (15)	DSPC (20) Cholesterol (55)	PEG-DSPE (10)
23	DODMA (15)	DSPC (20) Cholesterol (55)	PEG-amide-DSA (10)
24	DODMA (15)	DSPC (20) Cholesterol (55)	PEG-carbamate-DSA (10)
25	DODMA (15)	DSPC (20) Cholesterol (55)	PEG-succinimide-DSA (10)

037/037